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ORIGINAL ARTICLE

Evaluation of the safety, effectiveness, and health-related QOL impact of early rehabilitation in patients with nephrotic syndrome

Kohji Iwai[1,2] · Yasuhiko Hatanaka[2] · Tamiro kawaguchi[3] · Shin-ichi Araki[4]

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Abstract

Background The aim of this study was to evaluate the safety, effectiveness, and health-related QOL impact of early rehabilitation in patients with nephrotic syndrome.
Methods Subjects consisted of 23 patients with nephrotic syndrome who had previously received steroid treatment. Patients worked performed quadriceps resistance training and aerobic training 5 days per week for 5 weeks. Urinary protein, albumin (Alb), creatinine (Cre), and blood urea nitrogen (BUN) were monitored once every week over a 5-week period based on medical records. The 36-item short form health survey (SF-36) score was used to evaluate health-related QOL.
Results There was no significant difference in quadriceps force and no significant effect of age as shown by ANCOVA. Anaerobic threshold (AT) and peak oxygen consumption (peak VO_2) both increased significantly. AT was affected by the degree of change in body weight according to ANCOVA. Cre and BUN were not significantly altered. Urinary protein showed a significant decrease and Alb was significantly increased. Only physical function (PF) in the SF-36 showed a significant improvement following the intervention.
Conclusion Our data indicate that early rehabilitation involving quadriceps resistance training and aerobic training for nephrotic syndrome is safe and effective.

Keywords Nephrotic syndrome · Rehabilitation · Aerobic training · Quadriceps resistance training

Introduction

In Japan, approximately 13.3 million adults experience chronic kidney disease (CKD) according to a survey by the Japan Society of Nephrology [1]. Many patients show prolonged survival due to high healthcare standards in dialysis. Patients with CKD and undergoing dialysis demonstrate decreased physical exercise [2, 3], and a comprehensive program of kidney rehabilitation has been recommended for patients with disorders related to renal diseases and dialysis [4]. Accumulating evidence in kidney rehabilitation suggests an improvement of malnutrition–inflammation complex syndrome [5], promotion of assimilation of muscle protein [6], improvement of quality of life [7], and improvement of exercise capacity [8]. Most of these studies included patients with stable CKD and regular dialysis, rather than acute cases. There are no clear guidelines for acute cases; thus, there is a need for additional evidence regarding the effect of kidney rehabilitation on acute onset renal disease.

According to nephrotic syndrome guidelines in Japan, excessive rest is not advisable because a long period of bed rest increases the risk of deep vein thrombosis and pulmonary embolism [9]. This suggests that rest is a relative risk factor, and there is no clear statement on the safety and efficacy of early rehabilitation for nephrotic syndrome.

The purpose of this study is to examine the safety and effectiveness of an early common intervention approach involving 5 weeks of quadriceps resistance training and aerobic training in patients with nephrotic syndrome who received steroid treatment.

✉ Kohji Iwai
kojin@belle.shiga-med.ac.jp

1 Division of Physical Therapy, Rehabilitation Units, Shiga University of Medical Science, Otsu, Japan

2 Graduate school of Health Science, Suzuka University of Medical Science, Suzuka, Japan

3 Department of rehabilitation, Shiga University of Medical Science, Otsu, Japan

4 Department of nephrology, Shiga University of Medical Science, Otsu, Japan

Methods

Study design

Prospective observational study.

Participants

Thirty patients diagnosed with nephrotic syndrome received steroid treatment at our hospital, of which seven patients were discharged prior to completing the study. A total of 23 patients (age 52.4 ± 23.5 years; 14 men, 9 women) were enrolled. None of the patients were receiving dialysis treatment and all patients lived independently. Steroid treatment was started a dose of 45–60 mg, adjusted for patient age and weight. Rehabilitation for prevention of thrombosis and disuse syndrome was started under the direction of a doctor. The doctor and physical therapist performed evaluations by direct monitoring and indirectly using blood tests and urinalysis to ensure safety. Subjects were hospitalized and were provided supervised meals by a nutritionist. Baseline characteristics of the patients at the time of hospital admission are shown in Table 1. Of the 23 patients, 12 patients had minimal change nephrotic syndrome (MCNS), 9 patients had membranous nephropathy (MN), 1 patient had lupus nephritis, and 1 patient had rapidly progressive glomerulonephritis. All patients underwent renal biopsy and then started steroid treatment, followed by rehabilitation. Twelve patients received steroid treatment only, nine patients received steroid treatment and immunosuppressive therapy, and two patients received steroid treatment, immunosuppressive therapy, and LDL apheresis.

Table 1 Baseline characteristics of the patients at hospitalization

	All patients (*n* = 23)
Age (years)	52.4 ± 23.5
Gender (Men, %)	14 (60.9%)
Height (cm)	161.2 ± 7.7
Weight (kg)	61.9 ± 8.9
BMI (kg/m^2)	23.9 ± 3.6
Creatinine (mg/dl)	0.9 ± 0.3
BUN (mg/dl)	
Median (IQR)	18.4 (13.0–24.0)
Albumin (g/dl)	1.8 ± 0.6
Urinary protein (g/gCre)	10.2 ± 4.6
CRP (mg/dl)	
Median (IQR)	0.08 (0.30–0.15)

Characteristics of the subjects are shown as mean ± SD in the parametric data, and median in the non-parametric data

BMI body mass index, *BUN* blood urea nitrogen, *CRP* C-reactive protein, *IQR* interquartile range

Study protocol

All patients started rehabilitation promptly after steroid treatment, and measurement results were recorded for each patient. The study protocol consisted of resistance training and aerobic training performed 5 days per week for 5 weeks. The detailed protocol for this study was as follows.

Protocol 1

Isometric quadriceps force was measured using an isometric dynamometer (Isoforce GT-360, OG Wellness Co., Okayama, Japan). During the assessment, the foot was not weight bearing and the knee was passively drawn into 60° flexion by gravity. A soft cuff, attached via an adjustable non-elastic metal cord to a load cell, was fitted with Velcro just above the ankle. The isometric quadriceps force was measured twice for 3 s after practicing once, and the greater value was recorded [10]. Quadriceps resistance training in elderly people can be effective even at a low load [11]. After we measured the maximum quadriceps force, quadriceps resistance training with a load of 40–60% of the maximum quadriceps force, depending on the age of the patient, was performed using a dedicated machine (Leg Extension FS-50, Paramount, Los Angeles, CA, US). Subjects performed one set of ten repetitions during the machine training session in a seated position. Repetition consisted of a two-count concentric (lifting) phase, a slight pause, and a four-count eccentric (lowering) phase [5]. The frequency of training was adjusted for medium or higher fatigue, and training occurred 5 days per week for 5 weeks. Patients performed 20-min sessions of quadriceps resistance training, and maximum quadriceps force was measured initially and again after 5 weeks. Weight loss during the intervention was primarily a decrease in hydration due to diuresis. The quadriceps force was not divided by body weight, but rather was divided by the length of the lower limb (Nm).

Protocol 2

For cardiopulmonary exercise testing (CPET), patients were instructed to exercise maximally to symptomatic endpoints measured using an isokinetic ergometer (Aerobike 75XL, Minato Medical Science Co. Ltd., Osaka, Japan). A mask was placed covering the nose and the mouth, and the patient breathed through a non-rebreathing valve. Air was delivered to an O_2 and CO_2 analyzer (Aeromonitor 300S, Minato Medical Science Co. Ltd., Osaka, Japan). Breath-by-breath gas exchange measurement was performed, permitting continuous measurements of ventilation (VE), oxygen uptake (VO_2), and CO_2 production (VCO_2) on-line. The instrument was calibrated using reference gases before every test. During the test, a standard 12-lead ECG (Case, GE Healthcare, Wauwatosa, WI, US) was interfaced and heart rhythm was monitored continuously throughout the exercise test. Blood pressure was measured using a standard cuff sphygmomanometer at 1-min intervals. After stationary warm-up exercise at an equivalent of 15 W for 3 min, a ramp protocol with incremental steps equivalent to 20 W/min was used at a rate of approximately 50 rotations/min [12]. In addition, elderly subjects performed at 10 W/min. All subjects performed a cool-down, at the initial workload of the exercise protocol, for at least 3 min after the cessation of ramping exercise. From the ventilator data, anaerobic threshold (AT) and peak oxygen consumption (peak VO_2) were calculated. AT was measured by *V*-slope analysis and peak VO_2 was expressed as the highest attained VO_2 during the final ramping exercise. Exercise tests were supervised by an expert team consisting of a doctor and physical therapist. Patients underwent 15–20-min aerobic training sessions (Watt; AT-1 min) and training occurred 5 days per week for 5 weeks. CPET was measured initially and again after 5 weeks.

Protocol 3

For renal function, in addition to the basic information at hospital admission, urinary protein, albumin (Alb), creatinine (Cre), and blood urea nitrogen (BUN) were assessed once per week for 5 weeks based on medical records. Mean urine protein excretion was determined as the average amount of urinary protein excretion over 5 weeks.

Protocol 4

The 36-item short form health survey (SF-36) score was used to evaluate health-related quality of life (HRQOL) [13]. The SF-36 is a comprehensive scale for the measurement of HRQOL via a self-administered questionnaire and consists of 8 subscales comprising physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). Assessments were performed at baseline and again after 5 weeks.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 22 (IBM, New York, NY, US). Results were considered statistically significant if the two-tailed P value was less than 0.05. Data are shown as the mean ± SD, except for non-normally distributed variables, which are shown as the median. Baseline comparisons between body weight, quadriceps force, AT, and peak VO_2 were performed using paired t test after examining normally distributed variables by the Shapiro–Wilk test. Quadriceps force was adjusted for age, and AT and peak VO_2 were adjusted for the degree of change in body weight by ANCOVA. Spearman's correlation analysis of both groups combined was performed to determine the association between mean urinary protein excretion and the degree of change in quadriceps force. Alb, Cre, BUN, and urinary protein excretion over the 5 weeks of the study were examined by repeated one-way ANOVA and Bonferroni test. Bonferroni correction was performed for non-normally distributed variables. For five cases in which the urinary protein did not decrease to 3.5 g/gCre or less over the 5 weeks, Alb, Cre, BUN, and urinary protein excretion were additionally examined. The eight subscales of the SF-36 were analyzed by t test or Wilcoxon signed rank test.

Results

All cases completed the training successfully, but only one case showed vagal reflex after CPET. The mean patient weight significantly decreased by 4.6 kg after intervention. Quadriceps force was increased by 7.8 Nm after intervention, which was not a significant difference, and was not affected by age as determined by ANCOVA ($p = 0.308$, Table 2). AT and peak VO_2 improved significantly after intervention. AT adjusted by the degree of change in body

Table 2 Body weight, quadriceps force and cardiopulmonary exercise testing before and after intervention

	Before intervention	After intervention	p value	ANCOVA p value for age	ANCOVA p value for amount of change in body weight
Body weight (kg)	56.7 ± 9.0	52.1 ± 7.4	< 0.001		
Quadriceps force (Nm)	92.3 ± 30.3	98.3 ± 33.6	0.068	0.308	
Anaerobic threshold (AT; ml/min/kg)	9.1 ± 3.6	10.8 ± 4.6	< 0.001		0.043
Peak oxygen consumption (Peak VO_2; ml/min/kg)	15.4 ± 4.6	17.6 ± 5.6	< 0.001		0.158

Mean mean value, *SD* standard deviation, *ANCOVA* analysis of covariance weight was improved according to ANCOVA ($p = 0.043$, Table 2). There was a negative correlation between mean urinary protein excretion and the degree of change in quadriceps force ($r = -0.42$, $p = 0.047$, Fig. 1). Cre and BUN were not significantly altered. Urinary protein showed a significant decrease at each week after 2 weeks as compared with week 1. There was a significant decrease between week 2 and 4, and between week 2 and 5. Alb was significantly increased at each week after 3 weeks as compared with the week 1, and, Alb was significantly increased at all weeks after week 3 compared with week 2, as well as between week 3 and 5 (Fig. 2). In the 5 cases where urinary protein did not decrease below 3.5 g/gCre during the intervention, renal function did not show a significant difference (Fig. 3). Eight subscales of the SF-36 were examined before and after intervention. Only PF showed significant improvement, while there was no significant difference with the other subscales (Table 3).

Discussion

In our study, quadriceps resistance training and aerobic training were performed 5 days per week for 5 weeks to verify the effect of exercise in patients with nephrotic syndrome who received steroid treatment. Quadriceps force was not significantly affected, but AT and peak VO_2 showed significant improvement without deterioration of renal function due to early rehabilitation. We previously reported that this was related to urine protein excretion and the effect of muscle

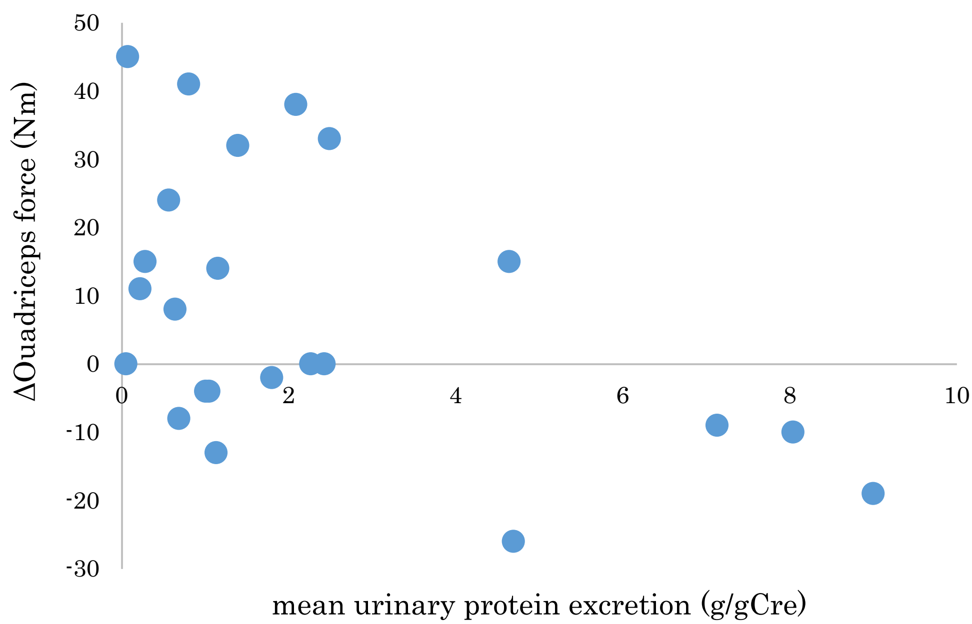

Fig. 1 Spearman's correlation analysis between mean urinary protein excretion and degree of change in quadriceps force (Δquadriceps force). $r = -0.42$; $p = 0.047$

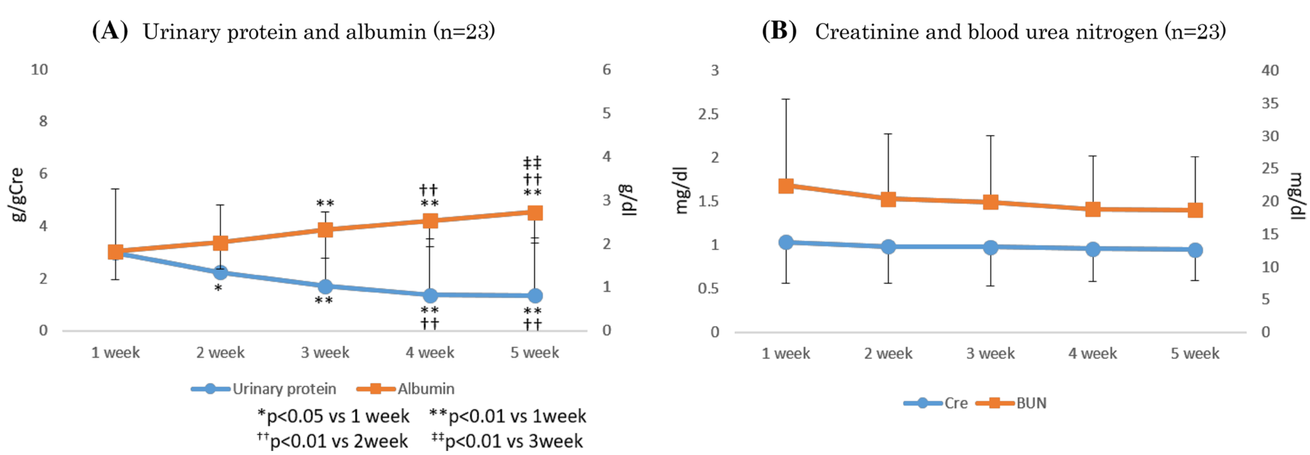

Fig. 2 Urinary protein and albumin over 5 weeks (**a**), creatinine and blood urea nitrogen (**b**), in patients with nephrotic syndrome

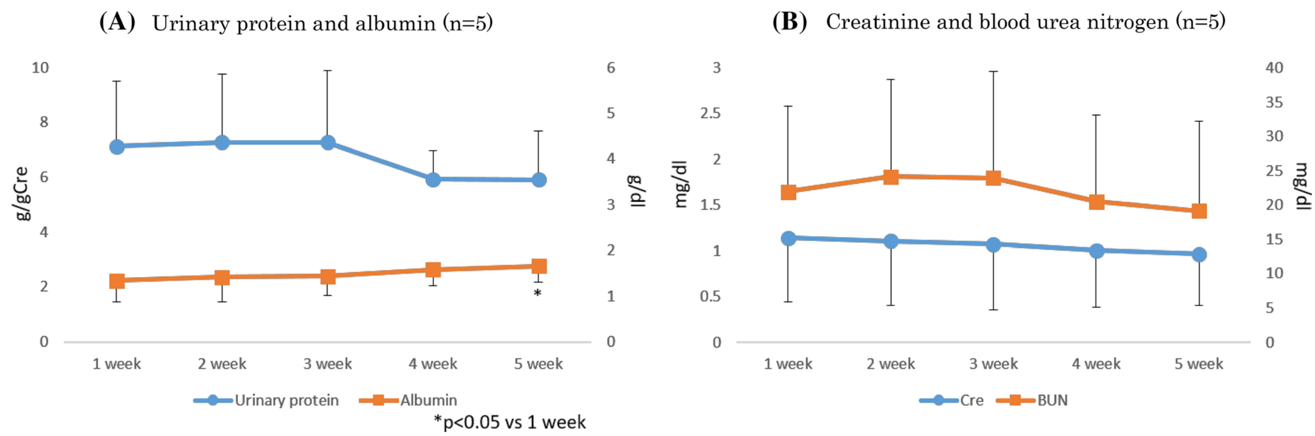

Fig. 3 Urinary protein and albumin over 5 weeks (**a**), creatinine and blood urea nitrogen (**b**), in patients with nephrotic syndrome at resistance to steroid treatment

Table 3 SF-36 scores (scoring method based on national standard value) before and after intervention

SF-36	Before intervention			After intervention			*p* value
	Mean ± SD	Median	IQR	Mean ± SD	Median	IQR	
PF	42.1 ± 13.0	41.1	30.5–51.6	46.7 ± 11.1	48.1	44.6–55.1	0.019
RP	38.9 ± 15.8	46.1	32.4–56.2	37.2 ± 13.8	39.2	29.0–52.8	0.141
BP	47.6 ± 14.1	52.6	35.8–61.4	50.7 ± 11.7	52.6	40.2–61.4	0.953
GH	44.2 ± 9.1	40.8	37.0–51.6	45.0 ± 7.6	46.2	38.1–48.9	0.606
VT	45.3 ± 14.1	50.2	37.9–56.4	49.8 ± 9.8	50.2	41.0–56.4	0.756
SF	39.2 ± 16.1	50.5	30.8–57.1	36.4 ± 13.5	37.4	30.8–50.5	0.236
RE	44.9 ± 14.9	52.3	35.3–56.6	42.6 ± 12.7	43.8	35.3–56.6	0.426
MH	47.4 ± 13.0	51.8	41.1–57.1	49.3 ± 10.7	49.1	41.1–59.7	0.958

Mean mean value, *SD* standard deviation, *median* median value, *IQR* interquartile range, *PF* physical functioning, *RP* role physical, *BP* bodily pain, *GH* general health perceptions, *VT* vitality, *SF* social functioning, *RE* role emotional, *MH* mental health

strengthening [14], and the present study also showed a similar result. It is likely that muscle strengthening was achieved more readily when urine protein excretion was reduced. It was difficult to strengthen muscle as a result of inhibition of muscle protein assimilation by protein catabolism due to increased urine protein excretion. Because there were differences in the effect of quadriceps resistance training depending on the subjects, there was no significant difference in the average quadriceps force.

The increased oxygen intake and energy production by aerobic training contributed to the improvement of exercise capacity. However, AT and peak VO_2 were divided by body weight in our analysis. In the case of nephrotic syndrome, decreased urinary protein, improvement of Alb to improve colloid osmotic pressure, increased intravascular volume, and the use of a diuretic resulted in increased urine output and decreased body weight. The average body weight decreased by 4.6 kg during the study. Decreased body weight leads to an increase in AT and peak VO_2. Therefore, AT and peak VO_2 were adjusted for the degree of change in body weight by ANCOVA. AT showed a significant improvement and there was no effect of change in body weight. These results demonstrated training effects of early rehabilitation. However, whether the effect of quadriceps resistance training contributed to exercise capacity could not be demonstrated in present study and remains to be addressed in a future study.

We performed blood tests and urinalysis to ensure safety with respect to renal function. Cre and BUN were not significantly affected during the intervention, while urinary protein showed a significant decrease. Alb was significantly increased along with the decrease in urinary protein. It is important to reduce proteinuria to delay progression to renal failure [15]. Safety was demonstrated by the absence of deterioration of renal function and increase of urinary protein during early intervention in patients with nephrotic syndrome. It has been reported that renal blood flow is not affected by aerobic training in healthy subjects [16], which may also be the case in nephrotic syndrome. Conversely, Miura et al. [17] reported the recurrence of MCNS due to an excessive walking load. However, the safety of exercise at an aerobic level in patients with nephrotic syndrome was demonstrated in the present study. Previous reports suggest that hypoalbuminemia is a risk factor for thrombosis [18] and decreased efficacy of diuretics [19], but our results support the safety of early rehabilitation, in that Alb showed a significant improvement throughout the duration of the study.

Certain types of patients with nephrotic syndrome show resistance to steroid treatment [20]. In refractory nephrotic syndrome, a sufficient effect is not observed even after 6 months or more of standard treatment. In this study, cases in which urinary protein did not decrease below 3.5 g/g Cre during intervention were defined as refractory. In total, 5 out of 23 cases fulfilled this criteria. Ji [21] demonstrated a trend for decreased urinary protein in response to treadmill exercise in a nephrotic mouse model. In our study, in which steroid treatment was performed in all cases, the possibility could not be excluded that steroid treatment masked harmful effects on renal function associated with early rehabilitation. Therefore, we reevaluated the change in renal function in five refractory cases that showed resistance to steroid treatment. For these cases, there was no significant deterioration in renal function, urinary protein, and Alb throughout the duration of intervention. Even considering the effect of steroid treatment, quadriceps resistance training and aerobic training appeared to be safe in patients with nephrotic syndrome in this study. However, the applicability of these findings is limited due to the small number of cases studied.

Assessment of HRQOL in this study was performed using SF-36 scores before and after the intervention. Among the eight subscales of the SF-36, PF was significantly improved, while there were no significant differences in the other subscales. The effect on social and mental health was not expected. Many of the subjects in this study were of productive age, and it is possible that anxiety about work and life, and relapses of nephrotic syndrome after discharge may not have been resolved.

There were some limitations to the present study. First, the study lacked a control group and was performed at a small single center. Additionally, only a small number of subjects were studied and the 5-week observation period was relatively short. Further studies using a larger number of subjects and a longer period of observation are needed. Second, safety was demonstrated based on resistance training and aerobic training, which is generally regarded as safe even for early rehabilitation; however, it is unknown from this study how much of a load can be considered safe in patients with nephrotic syndrome. Third, it is necessary to verify our findings in cases of acute kidney injury by nephrotic syndrome, nephrotic syndrome in children, and acute cases not treated with steroids due to chronically decreased renal function.

Conclusion

The present study evaluated the effect of quadriceps resistance training and aerobic training performed 5 days per week for 5 weeks in patients with nephrotic syndrome requiring steroid treatment. Blood tests showed no deterioration in renal function, urinalysis confirmed the safety of the intervention, and significant improvement in exercise capacity by resistance and aerobic training was demonstrated. With respect to HRQOL, only PF showed significant improvement, indicating an effect on physical QOL. Our results demonstrate that early rehabilitation with quadriceps resistance training and aerobic training for nephrotic syndrome is safe and effective.

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Compliance with ethical standards

Conflict of interest None of the authors have any conflicts of interest to declare in connection with this paper. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the clinical research ethical committee of Hospital of Shiga University of Medical Science (approval number: 27-187), and informed consent was obtained from all patients enrolled.

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